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09/386,709	08/31/99	BRAYDEN	D 99.1081.US

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EXAMINER	
GRASER, J	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/386,709	Applicant(s) Brayden
	Examiner Graser, Jennifer	Group Art Unit 1641

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits** is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 3, 9, 15 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 9, 15 and 19 are vague and indefinite because it is unclear what is encompassed by "enantiomers thereof" of copolymers of lactic acid and glycolic acid. The metes and bounds of the invention cannot be understood because it is unclear what would be considered an enantiomer of these acids.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1, 2, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Eldridge et al. (J. Controlled Release, 1990, 11: 205-214).

Eldridge et al disclose the preparation of biodegradable microspheres from various polymers, including poly(DL-lactide), poly(L-lactide) and poly (DL-lactide-co-glycolide), as carriers for the targeted delivery of vaccine antigens to the gut-associated lymphoid tissues. The microspheres were prepared by solvent-evaporation processes (page 206, column 2). Oral administration of these vaccine compositions was performed. Tissue penetration was specific to the Peyer's patches and was restricted to microspheres < 10um in diameter. Time-course studies on the fate of the poly (DL-lactide-co-glycolide) microspheres within the gut-associated lymphoid tissue showed that the majority of the microspheres less than 5 um in diameter were transported through the efferent lymphatics within macrophages (abstract). The absorption into the Peyer's patches of 1- to 10- um microspheres was performed (see page 208, column 2 and page 209, column 1). It is disclosed that based on the flexibility in bioerosion time, and thus vaccine release, of poly (DL-lactide-co-glycolide) copolymers, these microspheres were selected for further studies (page 209). It was selected as the most promising for application as an oral vaccine delivery system. Oral immunization with poly (DL-lactide-co-glycolide) microspheres containing a toxoid vaccine of staphylococcal enterotoxin B was performed. Size was found to be a determinant in controlling absorption. Microspheres less than 5um are predicted to induce a predominantly circulating antibody response based on their propensity to disseminate to systemic lymphoid tissues within antigen presenting accessory cells. All of the 1- to 10- um vaccines were found to be uniform spherical particles which were free of surface defects, contained a sufficient

amount of vaccine for convenient dosing and the bulk of the vaccine was released through biodegradation of the copolymer (see page 213, bottom of column 2).

5. Claims 1, 2, 3, 4, 5, 13, 14, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Jones et al (Infect.Immun., 1996, 64(2): 489-494).

Jones et al teach that fimbriae from *Bordetella pertussis* encapsulated in poly(lactide-co-glycolide) microparticles of a size appropriate for uptake by the immune inductive tissues of the gastrointestinal tract could protect mice from *B.pertussis* respiratory infection upon oral administration (abstract). It is disclosed that the mean diameter of the microparticles was 2.04um, with 90% of microparticles having diameters within the narrow range of 0.8 to 5.3 um (see page 490, Results section). The microparticles were prepared through a solvent extraction technique (top of page 490, column 1). It is further disclosed that analysis of the mechanism of particle uptake by M cells in mouse gut has clearly shown that this is restricted to materials with diameters less than or equal to 10um (page 492, column 2). It is further disclosed that smaller microparticles (1- to 10- um) were more immunogenic than larger particles (20- to 50- um), as the smaller microparticles were rapidly phagocytosed and distributed (page 290, column 1).

6. Claims 1, 2, 3, 4, 7, 9, and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Singh et al (Vaccine, 1998, 16(4): 346-352).

Singh et al disclose that diphtheria toxoid was encapsulated in microparticles prepared from polylactide-co-glycolide (PLG) polymers using a solvent evaporation technique (abstract). It is disclosed that rats were immunized with PLG microparticles containing the diphtheria toxoid

with all microparticles being less than 10um. Another group of mice were given microparticles of greater than 10um. See page 348, column 1. It is disclosed that the "mean size for the smaller microparticles was about **500nm**, the ideal size for phagocytosis by antigen presenting cells" (see page 350, column 1). It is disclosed that more potent antibody responses were induced with a single antigen in the microparticles rather than with two antigens in the same microparticles (page 350, column 2). It is disclosed that it was previously reported that more than one antigen in a multi-component vaccine may result in reduced immunogenicity for all the antigens (page 350, column 2). It is disclosed that the addition of alum with the microparticles gave the best response (page 350, column 2).

7. Claims 1, 2, 3, 4, 7, 8, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Hagan et al (US 5,603,960).

O'Hagan et al describe methods for producing microparticles useful in the formulation of pharmaceutical compositions. Methods of immunizing mammals against diseases comprising administering to the mammal an effective amount of antigen-containing microparticles. Vaccines comprising a pharmaceutical composition comprising said microparticles are also disclosed. It is disclosed that the preferred average microparticle size is between 200 nm and 200um (column 3, lines 33-34). It is disclosed that when the microparticles are to be orally administered, the preferred size of the microparticles is preferably between 100 nanometers to 10 um in size (column 7, lines 21-23). It is preferred that the microparticles be administered orally (column 3, lines 40-41). It is disclosed that the microparticles are preferably made with a biodegradable

polymer (column 4, lines 63-3). The solvent media used in the solvent evaporation method to produce the microparticles is dependent upon the material to be encapsulated (column 4, lines 60-63). The preferred polymer for encapsulating the bioactive material is a polylactide polymer, or particularly a polylactide-co-glycolide polymer (column 5, lines 24-30).

8. Claims 1, 2, 3, 4, 7, 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Uchida et al. (Biol. Pharm. Bull., 1994, 17(9): 1272-6).

Uchida et al teach oral delivery of poly(lactide-co-glycolide) microspheres containing ovalbumin (OVA) as vaccine formulations in order to study particle size and its effect on the immune response. Four kinds of OVA loaded PLGA microspheres with different mean average volume diameters (1.3, 4.0, 7.5, and 14.0 um) were manufactured using a w/o/w emulsion/solvent evaporation method (abstract). Single oral administrations of OVA loaded PLGA microspheres with different diameters to mice produced immune responses significantly higher than OVA solution as a negative control (abstract). The study revealed that the 4um microspheres produced the highest amount of antibody.

9. Claims 1, 2, 3, 4, 7, 8, 9 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Singh et al (Adv. Drug Delivery Reviews, 1998, 34: 285-304).

Singh et al teach methods of preparation and characterization of polymeric antigen delivery systems for oral administration. Singh et al disclose that a number of different polymers have been evaluated for the development of oral vaccines including naturally occurring, biodegradable polymers, such as starch, alginates, and biodegradable polymers, such as

polylactide-co-glycolides (PLG) (page 286, column 2). It is disclosed that the most commonly used polymers for solvent evaporation are PLG, which are biodegradable polymers with a long history of safe use in humans (page 287, column 2). It is further disclosed that solvent evaporation is the most widely used method for the preparation of microparticles with entrapped antigens (column 2, page 287). The reference teaches that for oral antigen delivery with PLG microparticles, the desired size range is usually less than 5 um (page 288, column 2). See page 291, column 2, which teaches that greater than 90% of the PLG microparticles have a mean size of less than 5 um. Polyamino acid microspheres are also taught which have sizes ranging from 0.1 to 5 um (page 296, column 2). This size includes microparticles which are less than 500nm. It is disclosed that these proteinoid particles appear to be targeted to the Peyer's patches due to their sub-micron size (page 297, top of column 1). It is disclosed that conflicting reports have appeared in the prior art concerning the optimal particle size for vaccine delivery and more work is needed to determine this size (page 300, bottom of column 1). However, for oral administration the literature is consistent with suggesting a size of less than 10 um, preferably less than 5 um, for uptake of the Peyer's patches to occur (page 300).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 7-11 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of O'Hagan et al (US 5,603,960)..

Jones et al teach that fimbriae from *Bordetella pertussis* encapsulated in poly(lactide-co-glycolide) microparticles of a size appropriate for uptake by the immune inductive tissues of the gastrointestinal tract could protect mice from *B.pertussis* respiratory infection upon oral administration (abstract). It is disclosed that the mean diameter of the microparticles was 2.04um, with 90% of microparticles having diameters within the narrow range of 0.8 to 5.3 um (see page 490, Results section). The microparticles were prepared through a solvent extraction technique (top of page 490, column 1). It is further disclosed that analysis of the mechanism of particle uptake by M cells in mouse gut has clearly shown that this is restricted to materials with diameters less than or equal to 10um (page 492, column 2). It is further disclosed that smaller microparticles (1- to 10- um) were more immunogenic than larger particles (20- to 50- um), as the smaller microparticles were rapidly phagocytosed and distributed (page 290, column 1).

However, Jones et al do not particularly exemplify vaccine compositions comprising nanoparticles of less than 600nm or less than 500nm in size wherein said nanoparticles comprise at least one antigen entrapped or encapsulated.

O'Hagan et al describe methods for producing microparticles useful in the formulation of pharmaceutical compositions. Methods of immunizing mammals against diseases comprising administering to the mammal an effective amount of antigen-containing microparticles. Vaccines

comprising a pharmaceutical composition comprising said microparticles are also disclosed. It is disclosed that the preferred average microparticle size is between 200 nm and 200um (column 3, lines 33-34). It is disclosed that when the microparticles are to be orally administered, the preferred size of the microparticles is preferably between 100 nanometers to 10 um in size (column 7, lines 21-23). It is preferred that the microparticles be administered orally (column 3, lines 40-41). It is disclosed that the microparticles are preferably made with a biodegradable polymer (column 4, lines 63-3). The solvent media used in the solvent evaporation method to produce the microparticles is dependent upon the material to be encapsulated (column 4, lines 60-63). The preferred polymer for encapsulating the bioactive material is a polylactide polymer, or particularly a polylactide-co-glycolide polymer (column 5, lines 24-30).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use nanoparticles less than 600nm or less than 500nm in size as taught by O'Hagan in place of the microparticles used in the methods of Jones in which the mean diameter of the microparticles was 2.04um, with 90% of microparticles having diameters within the narrow range of 0.8 to 5.3 um (see page 490, Results section) because Jones et al specifically disclose that analysis of the mechanism of particle uptake by M cells in mouse gut has clearly shown that this is restricted to materials with diameters less than or equal to 10um (page 492, column 2). and that smaller microparticles (1- to 10- um) were more immunogenic than larger particles (20- to 50- um), as the smaller microparticles were rapidly phagocytosed and distributed (page 290, column 1). O'Hagan teaches vaccine compositions comprising microparticles of 100nm to 10

um in size which are made of the same polymers as those of Jones and uses similar methods to produce the microparticles. Since Jones specifically teaches the use of smaller microparticles allows for a more rapid phagocytosis and distribution it would have been obvious to one of ordinary skill in the art at the time the invention was made to make the particles of Jones slightly smaller, i.e., less than 500 or 600nm, absent unexpected or unobvious results, because a person of ordinary skill in the art would expect such a microparticle to improve the immune response of the Jones method.

12. Claims 6 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Singh et al (Vaccine, 1998, 16(4): 346-352) or O'Hagan et al (US 5,603,960).

Singh et al disclose that diphtheria toxoid was encapsulated in microparticles prepared from polylactide-co-glycolide (PLG) polymers using a solvent evaporation technique (abstract). It is disclosed that rats were immunized with PLG microparticles containing the diphtheria toxoid with all microparticles being less than 10um. Another group of mice were given microparticles of greater than 10um. See page 348, column 1. It is disclosed that the "mean size for the smaller microparticles was about **500nm**, the ideal size for phagocytosis by antigen presenting cells" (see page 350, column 1). It is disclosed that more potent antibody responses were induced with a single antigen in the microparticles rather than with two antigens in the same microparticles (page 350, column 2). It is disclosed that it was previously reported that more than one antigen in a multi-component vaccine may result in reduced immunogenicity for all the antigens (page 350.

column 2). It is disclosed that the addition of alum with the microparticles gave the best response (page 350, column 2).

O'Hagan et al describe methods for producing microparticles useful in the formulation of pharmaceutical compositions. Methods of immunizing mammals against diseases comprising administering to the mammal an effective amount of antigen-containing microparticles. Vaccines comprising a pharmaceutical composition comprising said microparticles are also disclosed. It is disclosed that the preferred average microparticle size is between 200 nm and 200um (column 3, lines 33-34). It is disclosed that when the microparticles are to be orally administered, the preferred size of the microparticles is preferably between 100 nanometers to 10 um in size (column 7, lines 21-23). It is preferred that the microparticles be administered orally (column 3, lines 40-41). It is disclosed that the microparticles are preferably made with a biodegradable polymer (column 4, lines 63-3). The solvent media used in the solvent evaporation method to produce the microparticles is dependent upon the material to be encapsulated (column 4, lines 60-63). The preferred polymer for encapsulating the bioactive material is a polylactide polymer, or particularly a polylactide-co-glycolide polymer (column 5, lines 24-30).

However, neither Singh or O'Hagan specifically disclose vaccine formulations comprising 2 subpopulations of microparticles wherein each subpopulation comprises a different antigen entrapped or encapsulated by a biodegradable polymer.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that additional subpopulations of microparticles/nanoparticles comprising

different antigens could be administered as a vaccine formulation because multivalent vaccines comprising different antigens were well known in the art at the time the invention was made. Further, it was well known in the art at the time the invention was made that encapsulation of antigens to be used in oral administration provided a much greater immune response then when the antigens were given without encapsulation because the encapsulation protects the antigen from the gastric acids of the stomach and allows for better uptake by the GALT and Peyer's patches. Further, Singh specifically teaches that more potent antibody responses were induced with a single antigen in the microparticles rather than with two antigens in the same microparticles (page 350, column 2). Therefore, it would have been obvious to one of ordinary skill in the art to separately encapsulate different antigens in separate microparticles for administration together as it would allow for separate presentation of the antigens and would provide a more efficient immune response than when the antigens were encapsulated together which would effectively provide a more diverse immune response than one antigen alone.

13. Correspondence regarding this application should be directed to Group Art Unit 1641. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JENNIFER GRASER
PATENT EXAMINER